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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/996,275	11/28/2001	Frank R. Sharp	10738-29	2341

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 03/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/996,275	SHARP ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *January 18, 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-19 and 21-93* is/are pending in the application.

4a) Of the above claim(s) *18,19,23-28,30-37 and 43-93* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-17,21,22,29 and 38-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

1. The amendment filed January 18, 2006 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

"Further, as will be understood by a person of ordinary skill in the art, specific accession numbers represent the identity of the gene assigned that accession number on the priority filing date of the present application, as understood by a person of ordinary skill in the art.."

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Interpretation

2. The term "injury database" is defined in the specification as "a database comprising a pattern of expression (see page 13, lines 16-17)." The term "database" is not defined by the specification, but a database is a "organized collection of information". So any collection of information will meet this "database" limitation.

Claim Rejections - 35 USC § 112

3. Claims 1, 2, 4-17, 21-22, 29 and 38-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The use of Genbank accession numbers in claims renders the claims vague and indefinite because, unlike SEQ ID Nos, Genbank Accession numbers are not stable and

can be changed at any time. This variation is even evidenced by one of the species specifically noted by Applicant in Table 1, Genbank Accession No: AF073839, in which Genbank states "On Nov 16, 1999 this sequence version replaced gi:3288880. (see attached)" In this case, there was a change from 671 to 672 basepairs, so the sequence disclosed in the Genbank reference prior to filing is not the same as the sequence which is currently in Genbank under the accession number AF073839. As MPEP 2173 notes "The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent." Therefore as a preliminary matter, it is indefinite which sequence is intended in the claim, since both sequences are referred to by the Genbank Accession No. AF073839. Further, since the Genbank accession numbers used in the claims are capable of changing at any time, so is the claim scope. So the boundaries of the claim will change whenever Genbank makes a revision to a record. This is not in compliance with the requirement that the scope of the claim be definite. Consequently, these claims are vague and indefinite under 35 U.S.C. 112, second paragraph.

Response to Arguments – 112, second paragraph rejection

4. Applicant's arguments filed January 18, 2006 have been fully considered but they are not persuasive.

Applicant argues that by adding new matter to the specification Applicant has clarified the 112, second paragraph issue. This is not correct and the material added to the specification is not consistent with the Genbank Accession numbers in the

specification. For example, Applicant changed the specification to state that the accession numer represents the identity of a gene as of the priority date of the application. When Applicant argues that the "gross definition" of the gene does not change, this is not necessarily correct or even logically consistent with the disclosure of the specification. Not all of the accession numbers are limited to single genes. Genbank Accession No. AC002400 (at page 85, line 22 of the specification) is drawn to a sequence (in gi:2576344) of 138,839 nucleotides which appears to encode at least four independent proteins. None of these genes was identified in the original sequence published (in gi:2315841), which was 136,331 nucleotides in length. Applicant's newly added definition does not help this matter, because which gene is "the gene" understood as being referred to by this accession number to the ordinary practitioner.

All four of the genes in this BAC? One or more of the genes? The use of Genbank Accession numbers remains indefinite. Further, Genbank expressly recognizes this variability, noting "a new GI is assigned if the protein translation changes in any way" (see http://ncbi.nih.gov/Sitemap/samplerecord.html). Genbank also notes at the same webpage that "Accession numbers do not change, even if information in the record is changed at the author's request.". As shown by AC002400, cited in Applicant's specification, these are not irrelevant concerns. These specific changes occur in at least one of the hundreds of records cited by Applicant. Therefore, Applicant's arguments are not found persuasive and the 112, second paragraph rejection is maintained.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1-2, 4-6, 8, 9, 11-17, 21-22, 29 and 38-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Kostulas et al (Stroke (1998) 29:462-466).

Kostulas teaches a method of claims 1 and 38 of injury assessment in an individual (see abstract) comprising the steps:

(a) determining a pattern of expression exhibited by blood cells obtained from the individual (see page 463, column 1, subheading "preparation of blood MNC" and figures 1-3 and table I, where Kostulas determines the pattern of expression of the number of cells which express Il-8, MCP-1, MIP-1alpha and MIP-1beta),

(b) comparing the pattern of expression exhibited by the obtained blood cells to an injury database to assess the injury (see table 1, where expression of IL-8 was compared).

Wherein the pattern of expression comprises patterns of gene expression and wherein the database comprises disese specific injury databases (see table

1 where four different genes are compared, specifically IL-8, MCP-1, MIP 1 alpha and MIP 1 beta, where the table itself provides a pattern of gene expression that is a "collection of information" regarding ischemic stroke patients).

With regard to claim 2, Kostulas teaches analysis of stroke patients (see abstract).

With regard to claims 4, 39, Kostulas teaches the pattern of gene expression of Il-8 (see table 1).

With regard to claim 5, Kostulas teaches analysis of peripheral blood samples (see page 463, column 1).

With regard to claim 6, 21-22, 29, and 40, Kostulas forms a pattern of expression, which is elevated Il-8 levels and unchanged MCP-1 levels (see table 1).

With regard to claims 8-9, Kostulas teaches ranking the expression levels of the expressed mRNAs (see table 1).

With regard to claim 11, Kostulas performs statistical analysis to determine the P value (see page 463, column 2 and table 1).

With regard to claims 12-13, 15, 42, Kostulas teaches the use of chemokines and demonstrates that Il-8 is hypoxia induced (see table 1, Il-8 and page 462, column 2).

With regard to claims 13-17, Applicant has admitted that "In fact, the genes providing the data points are already in the public domain and the Applicants do not assert their novelty or patentability. (see page 4 of response on August 10, 2005)."

With regard to claim 41, Kostas teaches Ischemic stroke (see title).

7. Claims 1-2, 4-17, 21-22 and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Das et al (U.S. Patent 6,316,197)

Das teaches a method of claim 1 of injury assessment in an individual (see abstract where the injury is exposure to a toxic agent) comprising the steps:

(a) determining a pattern of expression exhibited by blood cells obtained from the individual (see figure 33B and column 3, lines 42-67),

(b) comparing the pattern of expression exhibited by the obtained blood cells to an injury database to assess the injury (see column 3, lines 42-67).

Where the pattern of gene expression of HCI and EIF-1 (see figure 33B and see column 12, line 56 to column 13, line 22, where Das teaches that dozens of genes in peripheral blood are responsive to SEB (which includes lipopolysaccharide) and to Anthrax).

With regard to claim 2, Das teaches analysis of anthrax infected blood (see figure 33B).

With regard to claims 4, Das teaches the pattern of gene expression of HCI and EIF-1 (see figure 33B and see column 12, line 56 to column 13, line 22, where Das teaches that dozens of genes in peripheral blood are responsive to SEB (which includes lipopolysaccharide) and to Anthrax).

With regard to claim 5, Das teaches analysis of peripheral blood samples (see column 12, line 56 to column 13, line 22).

With regard to claim 6, 20-22 and 29, Das forms a pattern of expression, (see column 3, lines 42-67 and column 12, lines 61-62 "We observed that the in vivo response reflected the pattern of altered gene expression that we had seen in vitro.").

With regard to claims 7, 10, Das teaches the steps of i) isolating RNA from the blood cells (see column 19, lines 40-41), ii) preparing a labelled probe using the isolated RNA (see column 21, lines 15-43), iii) applying the probe to a microarray (see column 21, lines 15-43) and iv) measuring the level of the RNA (see column 21, lines 15-43).

With regard to claims 8-9, Das teaches ranking the expression levels of the expressed mRNAs (see column 3, lines 42-67 and column 12, lines 61-62 "We observed that the in vivo response reflected the pattern of altered gene expression that we had seen in vitro.").

With regard to claim 11, Das teaches class prediction (see column 16, line 22, where genes acted as markers which "predicted" the pattern of illness).

With regard to claims 12-15, Das teaches the use of chemokines like interleukin 5 (a glycosylated protein) (see table 3) and interleukin 6 (see table 1).

With regard to claims 13-17, Applicant has admitted that "In fact, the genes providing the data points are already in the public domain and the Applicants do not assert their novelty or patentability. (see page 4 of response on August 10, 2005)."

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-2, 4-17, 21-22, 29 and 38-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kostulas et al (Stroke (1998) 29:462-466) in view of Lockhart et al (U.S. Patent 6,040,138) .

Kostulas teaches a method of claims 1 and 38 of injury assessment in an individual (see abstract) comprising the steps:

(a) determining a pattern of expression exhibited by blood cells obtained from the individual (see page 463, column 1, subheading "preparation of blood MNC" and

figures 1-3 and table I, where Kostulas determines the pattern of expression of the number of cells which express Il-8, MCP-1, MIP-1alpha and MIP-1beta),

(b) comparing the pattern of expression exhibited by the obtained blood cells to an injury database to assess the injury (see table 1, where expression of IL-8 was compared).

Wherein the pattern of expression comprises patterns of gene expression and wherein the database comprises disese specific injury databases (see table 1 where four different genes are compared, specifically IL-8, MCP-1, MIP 1 alpha and MIP 1 beta, where the table itself provides a pattern of gene expression that is a "collection of information" regarding ischemic stroke patients).

With regard to claim 2, Kostulas teaches analysis of stroke patients (see abstract).

With regard to claims 4, 39, Kostulas teaches the pattern of gene expression of Il-8 (see table 1).

With regard to claim 5, Kostulas teaches analysis of peripheral blood samples (see page 463, column 1).

With regard to claim 6, 21-22, 29, and 40, Kostulas forms a pattern of expression, which is elevated Il-8 levels and unchanged MCP-1 levels (see table 1).

With regard to claims 8-9, Kostulas teaches ranking the expression levels of the expressed mRNAs (see table 1).

With regard to claim 11, Kostulas performs statistical analysis to determine the P value (see page 463, column 2 and table 1).

With regard to claims 12-13, 15, 42, Kostulas teaches the use of chemokines and demonstrates that Il-8 is hypoxia induced (see table 1, Il-8 and page 462, column 2).

With regard to claims 13-17, Applicant has admitted that "In fact, the genes providing the data points are already in the public domain and the Applicants do not assert their novelty or patentability. (see page 4 of response on August 10, 2005)."

While Kostulas teaches the injury assessment method as discussed above, Kostulas does not teach the elements of claims 7 and 10 and does not teach application of the method to microarrays, which is a clear intent of the invention, though the limitation never currently appears in the claims.

Lockhart teaches a method of analyzing expression of nucleic acids whose expression is altered in a disease state (see column 10, lines 30-32) comprising the steps:

(a) determining a pattern of expression using a microarray (see column 9, lines 25-35) exhibited by blood cells (see column 11, line 48),

(b) comparing the pattern of expression to a database to assess the injury (see column 25, lines 18-25, for example).

With regard to claim 7, Lockhart expressly teaches teaches the steps of i) isolating RNA from the cells (see column 4, lines 8-10), ii) preparing a labelled probe using the isolated RNA (see column 3 and column 4, lines 8-11), iii) applying the probe

to a microarray (see column 4, lines 1-7) and iv) measuring the level of the RNA (see column 4, lines 54-67) (this method is also taught in columns 11-17 and example 1).

With regard to claim 10, Lockhart expressly teaches labeling the cDNA product (see column 13, lines 50-65, for example).

With regard to claims 12-15, Lockhart teaches the use of chemokines like interleukin 6, a glycosylated protein (see table 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use a microarray and microarray methods of Lockhart to analyze the gene expression in stroke as discussed by Kostulas since Lockhart notes "It will be appreciated that the methods of this invention can be used to monitor (detect and/or quantify) the expression of any desired gene of known sequence or subsequence. Moreover, these methods permit monitoring expression of a large number of genes simultaneously and effect significant advantages in reduced labor, cost and time. The simultaneous monitoring of the expression levels of a multiplicity of genes permits effective comparison of relative expression levels and identification of biological conditions characterized by alterations of relative expression levels of various genes. Genes of particular interest for expression monitoring include genes involved in the pathways associated with various pathological conditions (e.g., cancer) and whose expression is thus indicative of the pathological condition (see column 4, lines 54-67)." The ordinary practitioner, motivated by Kostulas to detect gene expression in stroke, would have been strongly motivated to use the microarray method of Lockhart to

determine which genes were involved in stroke in order to permit diagnosis as taught by Lockhart.

Response to Arguments – Prior art

11. Applicant's arguments filed January 18, 2006 have been fully considered but they are not persuasive.

Applicant presents a series of arguments regarding the meaning of the term "pattern of expression". Applicant correctly notes that page 15 defines this phrase, but then attempts to import additional elements into the definition such as the argument that a single molecule does not consitute an expression pattern. The specification definition at page 15 does not limit the patterns to multiple genes. In any case, each of the prior art references, Kostulas and Das use multiple genes, with Kostulas having four genes in Table 1 and Das referring to at least two genes. Where Applicant refers to page 17 in that 10 molecules are necessary, the specification actually states that in one embodiment of the invention "at least about 10" molecules are necessary. This language is not limiting.

While it is clear that Applicant disagrees with the interpretation of the claim, there is no structural element of the claim as distinguished from the specification, which expressly requires numbers of molecules or specific injuries. The current situation is more similar to the situation that the Federal Circuit discussed in In re Morris, where the Federal Circuit noted "Absent an express definition in their specification, the fact that appellants can point to definitions or usages that conform to their interpretation does not make the PTO's definition unreasonable when the PTO can point to other sources that

support its interpretation." In re Morris, 44 USPQ2d 1023, 1029 (Fed. Cir. 1997). In the current case, the definitions provided by Applicant are not limiting parts of the specification. The specification clearly uses the language of alternative embodiments. At page 15, the "pattern of expression" can even expressly encompass no change. The decision of the court in In re Bigio, 72 USPQ2d 1209 (Fed. Cir. 2004) strongly supports the breadth of interpretation. That court notes "Nevertheless, this court counsels the PTO to avoid the temptation to limit broad claim terms solely on the basis of specification passages."

In concert with Morris and Bigio is the decision in In re American Academy of Science Tech Center, 70 USPQ2d 1827, 1834 (Fed. Cir. 2004), where the Federal Circuit noted "We have cautioned against reading limitations into a claim from the preferred embodiment described in the specification, even if it is the only embodiment described, absent clear disclaimer in the specification." Applicant would like to read the preferred embodiment into the claims. Based upon Bigio and In re American Academy of Science Tech Center, and the 1997 Morris decision, the Federal Circuit is quite clear that absent a clear disclaimer, which is not present in this case, the broadest reasonable interpretation should be applied to the claims.

The specific references of Kostulas and Das teach specific patterns of expression which are compared between normal and ill patients. This comparison, whether in table form or in the text of the reference, suffices to properly anticipate the claims.

Applicant reiterates the arguments regarding Kostulas for the 103 rejection. Since this argument was not found persuasive in the 102 rejection, it is also not found persuasive for the same reasons in the 103 rejection, which is therefore maintained.

Conclusion

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637
2/28/06